To model or not to model?

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ABSTRACT **In theory, the combination of mathematical modeling with experimental studies can be a powerful and compelling approach to understanding cell biology. In practice, choosing appropriate problems, identifying willing and able collaborators, and publishing the resulting research can be remarkably challenging. To provide perspective on the question of whether and when to combine modeling and experiments, a panel of experts at the 2010 ASCB Annual Meeting shared their personal experiences and advice on how to use modeling effectively.**

Unlike Shakespeare's Hamlet, who pondered a somewhat weightier quandary, the answer to the question of whether modeling can improve the quality and impact of experimental work in cell biology seems increasingly clear: Yes. After all, mathematical models based on the physical principles that cells and molecules must follow have the potential to enrich experimental studies, guide data interpretation, and make testable predictions. Given that our intuition about how objects behave generally fails at the scale of cells and molecules (How far does an *Escherichia coli* bacterium coast after it stops swimming?), we must rely on mathematical models to reveal what we ought to expect. Most scientists recognize the benefits of a close interplay between modeling and experiment, but studies that effectively combine the two continue to be rare. Why?

A *Molecular Biology of the Cell* (*MBoC*)-sponsored workshop explored the promises and perils of linking experiments with models before an audience of greater than 200 at the ASCB's 50th anniversary meeting in Philadelphia this past December. Panelists Kerry Bloom (UNC Chapel Hill), Julie Theriot (Stanford University), Leah Keshet (University of British Columbia), Tom Rapoport (Harvard Medical School), and Eric Wieschaus (Princeton University) shared their personal experiences bridging what can sometimes appear to be a wide gulf between the collection of quantitative data using laboratory equipment and the use of mathematics and computers to establish causal relationships between those quantities and a biological outcome.

The panelists began by describing examples from their own research that combined experiments and modeling, such as three-dimensional physical models of mitosis, metabolic control analysis, and the bicoid morphogen gradient. In ideal cases, models can play an essential role in revealing the mechanistic basis of biological processes by showing that understandable physical phenomena underlie seemingly confusing data. Even in less ideal cases, when models do not fully explain the experimental data, the process of making mental models explicit by writing them down in mathematical form can force new ideas to the forefront and spur insight. Indeed, demonstrating with the help of a model that the standard ideas or prevailing dogma do not explain a set of experimental data can be the beginning of an exciting search for the real mechanism.

Although uniformly supportive of modeling and its value in cell biology research, the panelists had words of caution as well: Not all models are helpful, and not all attempts to combine experiments and modeling will yield insight. Often, extensive experience is necessary to choose suitable experimental questions to model, decide on the appropriate level of modeling, and identify the right collaborators. For senior investigators, this remains a challenge; for junior investigators, it can seem virtually impossible to master all of the background knowledge and connections needed for a successful collaboration. So what steps can be taken?

To help researchers at all career stages, the panelists provided advice about how to start and maintain research projects that link experiments and modeling. This advice, often inspired by questions from the audience during the open discussion at the workshop, is summarized below.

WHO SHOULD BE DOING MATHEMATICAL MODELING?

In short, everyone. Just as restriction enzymes were specialized experimental tools in the 1970s and have now become part of the standard tool kit of cell biologists, basic mathematical modeling should become part of the standard tool kit of cell biologists. There will continue to be the need for experts that push the frontiers in mathematical modeling, but there is every reason for experimentalists themselves to be able to model a diffusion gradient or calculate stress and strain. Software packages that simplify the

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process of making calculations and constructing models are readily available today. With basic training often available online, simple modeling to check assumptions, guide experiments, and analyze data can and should become part of routine laboratory work. As the scope of modeling increases in complexity or requires more advanced and specialized approaches, seek out a collaborator.

HOW DO I FIND THE RIGHT COLLABORATOR?

Carefully. Identifying the right person for a modeling collaboration is the key to a successful and enjoyable experience. Take time to find someone with whom you get along well and who has the patience to handle the many twists and turns a collaborative project linking experiments and modeling can take. Conferences such as the annual meeting of the ASCB can be excellent venues for identifying modelers interested in biological questions, and advice from colleagues can direct you to an expert with an open mind and an interest in new challenges. Keep in mind that you are both in for a wild ride as the limitations of data collection in experiments collide with the mathematical model's need for specific quantities and precise values. Not surprisingly, the cultures of full-time experimentalists and professional modelers are different, and so are the scientific problems that generate excitement and the expectations for sharing of reagents and codes. But if you succeed in identifying an interesting biological problem where both modeling and experiments are needed to reveal new insight, the collaboration can be fruitful and rewarding for many years to come.

DOES ALL EXPERIMENTAL WORK NEED MODELING?

No. Some research is still at a descriptive stage, where the essential elements needed to form the basis of a mathematical model are still being sought. Some research is already at a quantitative stage, where locations and concentrations of molecules can be measured, for example, but the number of unknown variables is so large that any model would contain so many assumptions that it would fail to provide any real insight. Certainly the goal of combining modeling and experiments is not to have an equation that simply fits the experimental data; rather, the goal is to gain mechanistic insight into a problem based on the ability of a model to exclude alternate explanations. Used properly, mathematical models can put competing hypotheses into a rigorous framework, explain paradoxical data, or constrain molecular mechanisms. As molecular biology of the cell advances, these uses of modeling will only become more important and may one day become an expected part of studies that purport to reveal a mechanism. However, there is still room in cell biology for pure modeling without experimental work, provided it meets the basic standard of advancing our understanding of a biological process.

HOW DO I PUBLISH PAPERS THAT COMBINE EXPERIMENTS AND MODELING?

Publishing articles combining experiments and modeling is not easy, but it is getting better. During the workshop, panelists and audience members shared examples of research projects that were derailed at the publication stage due to difficulties associated with including both experimental and computer simulation components in a single paper. However, as more journals like *MBoC* recognize the value of combining experiments and modeling, more opportunities for publishing collaborative work will arise. Such collaborative papers must not only meet the basic standard of advancing understanding but must also communicate the mathematical model and its interpretation effectively to the intended biological audience. Meeting both requirements has been particularly difficult given the lack of common standards for modeling papers. To address this, a team of *MBoC* associate editors has compiled a list of guidelines for publishing papers containing theory and modeling that describes the expectations of this journal; these are described in an accompanying editorial (Mogilner *et al*., 2011). Broader acceptance of such guidelines will be an important step toward encouraging the use of mathematical modeling, together with experiments, to make our understanding of cell biology more precise and, quite literally, "by the numbers."

REFERENCE

Mogilner A, Edelstein-Keshet L, Bloom K (2011). Guidelines for publishing papers containing theory and modeling. Mol Biol Cell 22, 907–908.